PHARMACOLOGIC ANALYSIS OF MNEMIC DISTURBANCES OF VARIED GENESIS

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KEY WORDS: amnesia; piracetam; meclofenoxate; nicergoline; memory trace.

A traditional approach to the control of memory functions and learning in experimental research is to use psychopharmacologic agents which, it is considered, are modulators of endogenous regulators of these functions [1]. The most promising group of compounds optimizing mnemic processes are currently various nootropic agents differing in structure and mechanism of action, and whose qualitative differences from other psychotropic drugs are exhibited most clearly under conditions interfering with higher nervous activity and, in particular, in experimental amnesias of varied genesis [7, 9, 11]. According to the adaptation concept of memory, information about different events is consolidated by a mechanism of adaptation of the synapsis to excitation that is nonspecific with respect to information [2].

In this connection the hypothesis that there exists a common neurobiological mechanism, which lies at the basis of memory disturbances, resulting from different procedures, is of great interest [8]. To analyze this hypothesis, the effect of nootropic drugs differing in their structure and mechanism of action on mnemic disturbances of varied genesis was studied.

EXPERIMENTAL METHOD

The investigation was conducted on noninbred male albino mice weighing 18-22 g. Training was carried out by the passive avoidance conditioned reflex (PACR) method in a two-compartment box with dark and light compartments, and with nociceptive stimulation applied in the dark compartment [6]. When recall was tested 24 h after training the animal was placed in the light compartment of the box and the latent period (LP) of the first visit to the dark compartment and the length of stay (LS) in the light compartment in the course of 2 min were recorded. Three models of experimental amnesia were used. Maximal electric shock (MES) was applied immediately after the training session through corneal electrodes [7]. The muscarinic cholinolytic scopolamine (2.5 mg/kg) was injected intraperitoneally in isotonic NaCl solution 15 min before the training session [5, 10]. Phenazepam (2 mg/kg) was injected intraperitoneally in a suspension with Tween-80, 30 min before the training session. The nootropic drugs were injected intraperitoneally 50 min before formation of PACR: piracetam (α-pyrrolidone acetamide) in a dose range of 200-800 mg/kg, meclofenoxate in doses of 50 and 100 mg/kg, and nicergoline in doses of 1-4 mg/kg. Control animals received isotonic NaCl solution. The data were subjected to statistical analysis by parametric and nonparametric tests [4].

EXPERIMENTAL RESULTS

Control animals receiving NaCl solution before training in PACR showed stable recall of the reflex 24 h later (Figs. 1-3). The use of MES immediately after training in PACR led to a definite lowering of the values of LP and LS during recall (Fig. 1). Piracetam exhibited antiamnesic properties starting with a dose of 300 mg/kg, but a smaller dose was ineffective. Meclofenoxate, in doses of 50 and 100 mg/kg, had marked protective properties; the values of LS, moreover, exceeded the corresponding values in the control group without the use of the amnesic factor. It was shown that with an increase in its dose meclofenoxate

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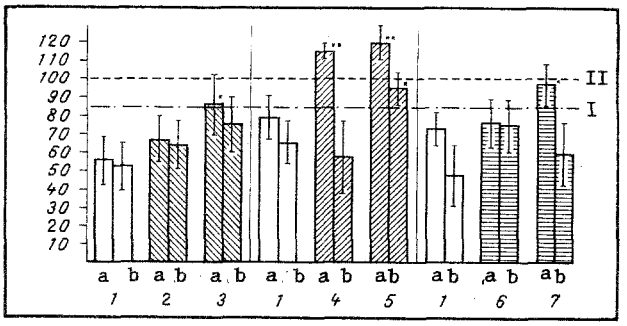

Fig. 1. Amnesia induced by MES. Ordinate, time (in sec). I) LP during recall in control without amnesic factor; II) LS during recall in control without amnesic factor; a) LS during recall; b) LP during recall. 1) Control (MES); 2) piracetam 200 mg/kg + MES; 3) piracetam 300 mg/kg + MES; 4) meclofenoxate 50 mg/kg + MES; 5) meclofenoxate 100 mg/kg + MES; 6) nicergoline 1 mg/kg + MES; 7) nicergoline 4 mg/kg + MES. Here and in Figs. 2 and 3: *p < 0.05, **p < 0.001.

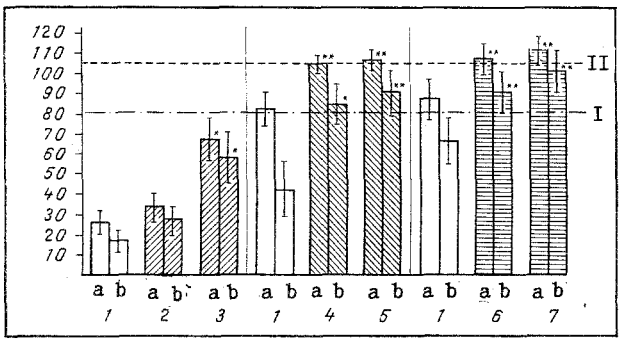

Fig. 2. Amnesia induced by scopolamine. Legend as to Fig. 1. 1) Control (scopolamine 2.5 mg/kg); 2) piracetam 400 mg/kg + scopolamine 2.5 mg/kg; 3) piracetam 800 mg/kg + scopolamine 2.5 mg/kg; 4) meclofenoxate 50 mg/kg + 2.5 mg/kg; 5) meclofenoxate 100 mg/kg + scopolamine 2.5 mg/kg; 6) nicergoline 1 mg/kg + scopolamine 2.5 mg/kg; 7) nicergoline 2 mg/kg + scopolamine 2.5 mg/kg.

caused a sharp rise in the values of LP, whereas those of LS did not depend on the administered dose. Nicergoline had marked antiamnesic properties in a dose of 4 mg/kg, under the influence of which the values of LS increased whereas LP was unchanged. Reduction of the dose to 1 mg/kg caused disappearance of this effect.

Investigation of the effectiveness of the drugs in animals with scopolamine-induced amnesia showed that piracetam in a dose of 400 mg/kg did not prevent the development of retrograde amnesia, as shown by the values of LP and LS, which did not significantly exceed values in the control group (Fig. 2). However, increasing the dose to 800 mg/kg led to the antiamnesic properties of the drug being clearly exhibited, in the form of a significant increase in the values of LS and LP, despite administration of the amnesia-inducing agent. Meclofenoxate in doses of 50 and 100 mg/kg had a distinct protective action and completely prevented the development of scopolamine amnesia, with an increase in both LS and LP during recall. Under the conditions of this model of amnesia, incidentally, the effect of the drug did not depend on dose. Nicergoline, in doses of 1 and 2 mg/kg, in scopolamine-induced amnesia, also exhibited marked protective properties, increasing the values of the two parameters characterizing antiamnesic activity.

Administration of phenazepam in a dose of 2 mg/kg before the training session in PACR led to distinct amnesia with respect to the skill, as shown by a significant fall in the values of LP and LS during recall (Fig. 3). Piracetam (800 mg/kg) prevented the development

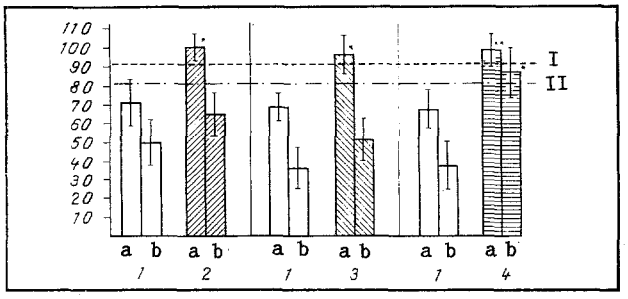

Fig. 3. Amnesia induced by phenazepam. Legend as to Fig. 1. 1) Control (phenazepam 2 mg/kg); 2) piracetam 800 mg/kg + phenazepam 2 mg/kg; 3) meclofenoxate 100 mg/kg + phenazepam 2 mg/kg; 4) nicergoline 4 mg/kg + phenazepam 2 mg/kg.

of amnesia induced by phenazepam, and values of LS during recall were actually greater than the corresponding values for the control group without the use of the amnesic factor. The antiamnesic activity of meclofenoxate (100 mg/kg) under the conditions of this experimental model of amnesia was comparable with that of piracetam. Nicergoline (4 mg/kg) had a marked protective action, increasing both LS and LP sharply during recall.

It can thus be concluded from these experiments that under the conditions of different models of amnesia all the nootropic drugs tested exhibited definite protective properties. Depending on the type of amnesia, the depth of the effect of the preparations varied a little. For instance, in amnesia induced by MES, the most profound antiamnesic effect was obtained with meclofenoxate, in scopolamine-induced amnesia by meclofenoxate and nicergoline, whereas in amnesia induced by phenazepam, the effect of all the nootropic drugs tested was similar.

The fact that preparations with different biochemical and molecular mechanisms of action have marked antiamnesic properties is evidence in support of the hypothesis of a possible common neurobiological mechanism lying at the basis of memory disturbances induced by various factors. Irrespective of the intimate mechanism of action of a particular drug, improving the learning process and short-term memory, at the structural level a single system of intracentral regulation is formed, and nonspecificity of the neurotransmitter involved in engram formation evidently lies at the basis of the feedback mechanisms responsible for the adaptive character of changes in bodily functions [2].

It is nowadays considered that amnesia for skill is the result of a disturbance of recall [2, 3]. According to Kruglikova [5], a conditioned connection which is fixed against the background of the action of scopolamine is equivalent to an initially weak conditioned connection, and the conditioned connection formed is converted into a state below the threshold for counting. It can also be postulated that the amnesia-inducing effect of phenazepam is due to prevention of memory trace formation through weakening of the negative unconditioned reinforcement under the conditions of passive avoidance conditioning, i.e., by the creation of conditions when the memory trace is below the threshold of recall. In view of the arguments given above it can be postulated that the neurophysiological mechanisms of and antiamnesic action of nootropic drugs is linked with directional activation of a weakened engram of varied etiology, which lies below the recall threshold and its conversion into a form amenable to recall.

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ABILITY OF 1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE AND SOME OTHER PYRIDINE DERIVATIVES TO CAUSE PARKINSONISM

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The compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) gives rise to clinical features of parkinsonism (akinesia, rigidity, tremor) and also to lowering of the dopamine (DA) level in the brain and to degeneration of neurons of the substantia nigra (SN), characteristic of this disease, in man and monkeys [6, 10]. The mechanism of action of MPTP is linked with a number of consecutive processes: oxidation to 1-methyl-4-phenylpyridinium (MPP^+) under the influence of monoamine oxidase, uptake of MPP^+ by the retrograde transport system of DA into neurons, binding with neuromelanin, and inhibition of various intracellular processes, including oxidative phosphorylation in mitrochondria [12].

The widespread distribution of various pyridine derivatives, which can be regarded as structural analogs of MPTP and MPP^+, as waste and end products of the chemical industry raises the question of a possible link between the prevalence of idiopathic parkinsonism and the use of compounds of this sort in practice. We know [5] that the intensity of application of the herbicide paraquat (1,1-dimethyl-4,4'-dipyridinium dichloride) correlates with the prevalence of parkinsonism in some provinces of Canada.

The development of laboratory methods of assessment of the MPTP-like action of various chemical compounds and testing of some known and newly synthesized pyridine and dipyridyl derivatives, which are potential pesticides, for these properties are thus matters of urgency.

EXPERIMENTAL METHOD

Male C57BL/6 mice weighing 22-25 g were used at different times of the year. The substances for testing, in doses close in acute toxicity to LD_{50}, were injected intraperitoneally in 0.1 ml of physiological saline daily. Control animals received the same volume of physiological saline. Some of the animals were left for 2 months to allow the development of a behavioral syndrome to be observed. Animals of the other group were killed a few days after the injection by cervical dislocation, the brain was removed, and concentration of DA, noradrenalin (NA), and serotonin (5-HT) were determined spectrofluorometrically [1]. The significance of the measurements of the DA, NA, and 5-HT concentrations was determined by Student's test. Pyridine derivatives were synthetized in the writers' institute and their

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